Standards for federally sponsored international clinical research– An introduction

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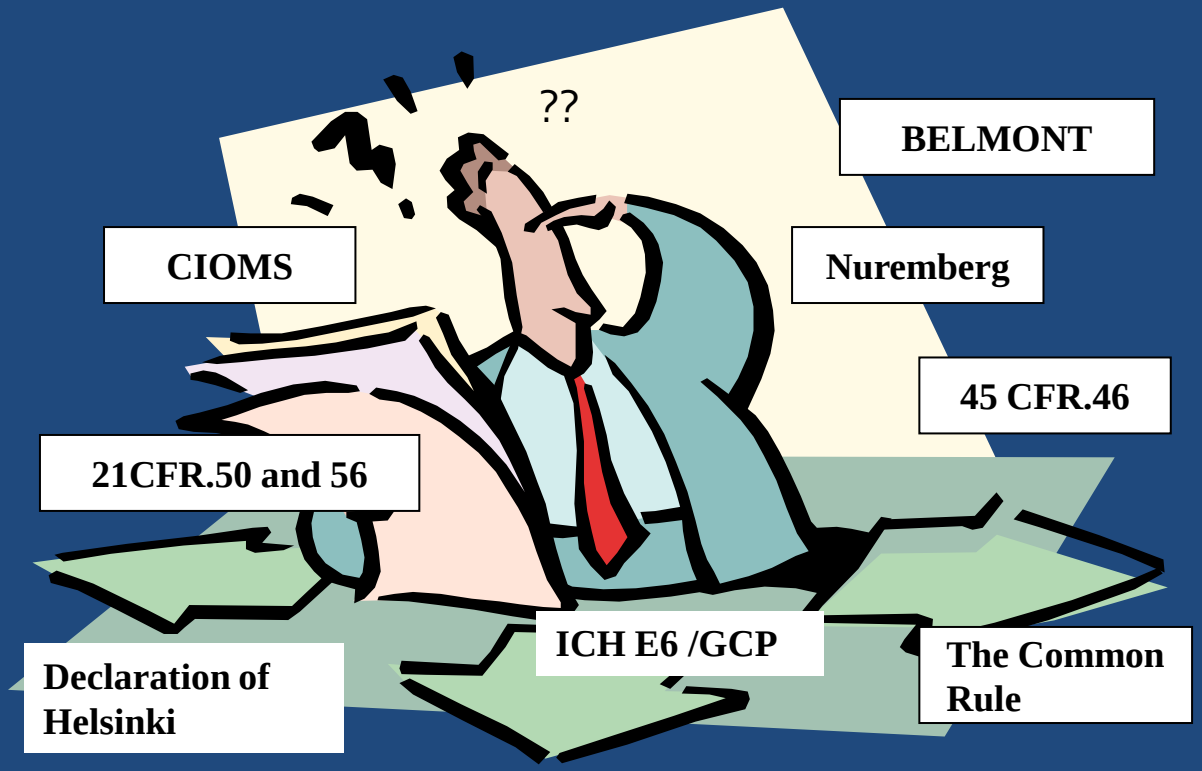
Standards for U.S. federally sponsored international clinical research

- The Common Rule
- U.S. FDA regulations/ GCP and ICH/GCP
- Clinicaltrials.gov
- Agency specific policies and guidance
- Legal and ethical requirements of collaborating and host jurisdiction(s)
- International guidance, e.g. CIOMS, Helsinki, and others

Standards for U.S. federally sponsored international clinical research



The U.S. Common Rule

- Federal Policy for the Protection of Human Subjects
- Currently followed by 17 federal agencies*
  - e.g. DHHS- 45CFR Part 46; VA – 38 CFR Part 16; USAID -- 24 CFR Part 60, others

U.S. Common Rule-DHHS

- Title 45 US CFR.46
  - Subpart A- Basic DHHS Policy for Protection of Human Research Subjects
  - Subpart B- Pregnant women, human fetuses, and neonates
  - Subpart C- Prisoners
  - Subpart D- Children
  - Subpart E- IRB Registration

http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html

45CFR.46 Protection of Human Subjects (Subpart A, Common Rule)

- Two "pillars" of human subjects protection:
- Independent review
  - Composition and function of a local institutional review board (IRB)
- Informed consent
  - Basic elements, documentation requirements, waiver criteria

45CFR.46 Protection of Human Subjects (Subpart A, Common Rule)

- Criteria for IRB approval of research (45CFR.46.111)
  - **Risks are minimized**, consistent with sound research design
  - **Risks are reasonable** in relation to expected benefits, if any, and the importance of the knowledge reasonably expected
  - **Subject selection is equitable**, and
  - **Informed consent** will be sought from each subject or LAR and appropriately documented.
  - Adequate provisions for **monitoring**
  - Adequate provisions for protecting **privacy and confidentiality**
  - Additional protections for subjects likely to be **vulnerable** to coercion or undue influence

Assurance of Compliance with Federal Common Rule

- Office of Human Research Protections (OHRP) http://www.hhs.gov/ohrp
- Federal Wide Assurance (FWA)
- Documents institutional commitment to comply with the Common Rule

FDA REGULATIONS-Protection of Human Subjects

- 21CFR.50 Protection of Human Subjects (informed consent)
- 21CFR.56 Institutional Review Boards
- Other related FDA regulations, e.g.
  - 21CFR.312 Investigational New Drug Application
  - 21CFR.812 Investigational Device Exemption

http://www.fda.gov/oc/gcp/regulations.html

FDA and International Conference on Harmonization/Good Clinical Practice Guidelines

- Good Clinical Practice: Consolidated Guideline (1997) of the International Conference on Harmonisation (E6-(R1) - ICH/GCP "…an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects"
- Goals: Harmonize technical procedures and standards; improve quality; speed time to market
- FDA endorsed ICH/GCP in 1997
- ICH guidelines have been adopted into law in several countries (the 'de facto' global standard)
- Used as guidance for the FDA in the form of GCP

http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html

Standards for US supported research

- Registration in ClinicalTrials.gov
- FDA Amendments Act of 2007 or FDAAA, Title VIII, Section 801 mandates that a "responsible party" …register and report results of certain "applicable clinical trials"

Standards: Agency specific guidance; e.g. NIH

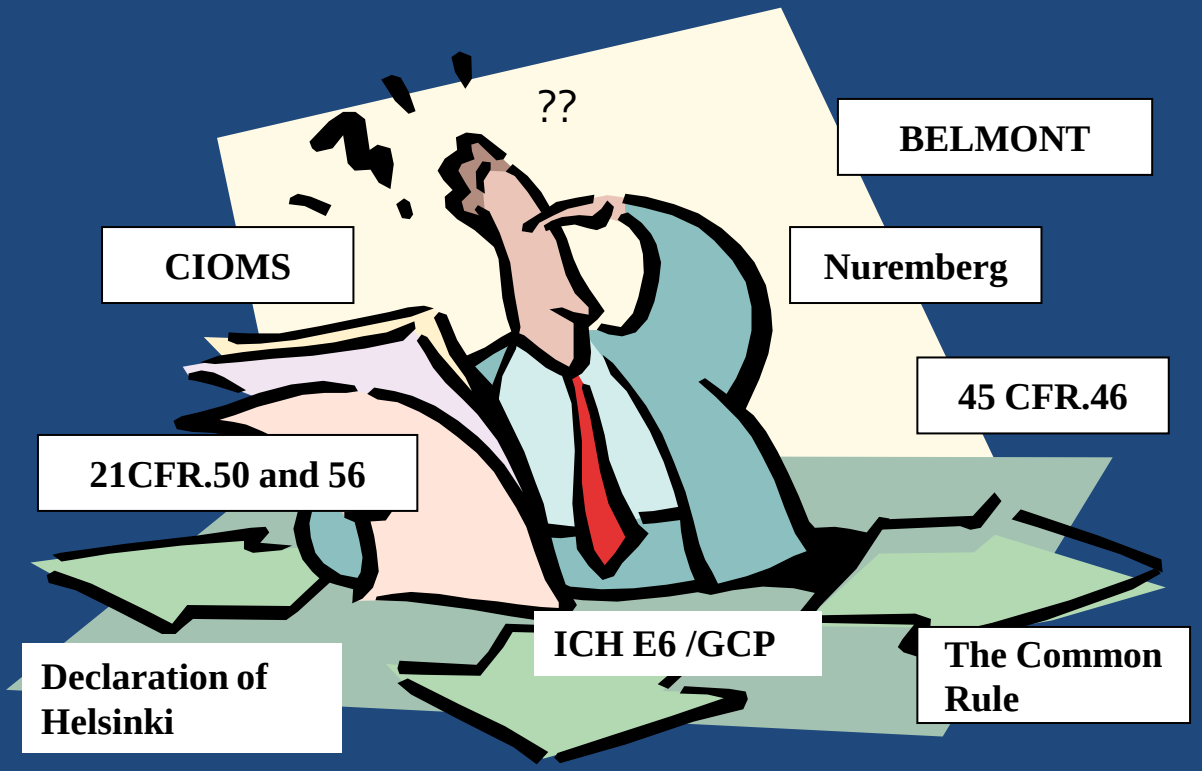
- NIH guidelines on the inclusion of women and minorities
- NIH Guidelines on the Inclusion of Children
- Data and Safety Monitoring Plans

http://grants.nih.gov/grants/policy/policy.htm

International Guidance

- National regulations and laws in collaborating jurisdictions
- Nuremberg Code
- Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects, World Medical Association
- International Ethical Guidelines for Biomedical Research Involving Human Subjects, Council for International Organizations of Medical Sciences CIOMS/WHO
- Universal Declaration on Bioethics and Human Rights, UNESCO

Standards for protection of research subjects



Standards: Current challenges

- Harmonization
- Burden
- Effectiveness
- Collaboration and respect

Current challenges: Harmonization

- Different content
  - e.g. waiver of consent; compensation for injury
- Different purview
  - e.g. US supported research, investigation of FDA regulated products, guidance
- Divergent interpretations
  - e.g. undue inducement, minimal risk, responsiveness, etc

Current challenges: Burden

- The number of rules and guidelines
- Disincentive to do clinical research or incentive to seek least burdensome path
- Delay
- Hinder otherwise ethically appropriate research?

Current challenges: Effectiveness

- Rules alone cannot protect research participants

  Need quality science, responsible engaged researchers and teams, carefully applied ethical principles, engagement of participants and communities…

- "The mere formulation of ethical guidelines for …research involving human subjects will hardly resolve all moral doubts that can arise…" CIOMS 2002

Current challenges: Effectiveness

- Insufficient guidance re: critical and complex issues (and disagreement)
  - E.g. Relevance of background conditions and injustices, what is owed to participants and to communities, etc.
- Inconsistencies in implementation

Current challenges: Collaboration and respect

- Collaboration
- Equivalent protections
- Capacity development
- Community engagement

- Ethical responsibility to protect the rights and welfare of research participants and communities in research

- Ethical responsibility to advance the good of societies, communities, and research participants through research